Molecular Testing for Lipomatous Tumors: Critical Analysis and Test Recommendations Based on the Analysis of 405 Extremity-based Tumors

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Abstract: Ancillary molecular testing has been advocated for diagnostic accuracy in the differentiation of lipomas from atypical lipomatous tumors/well-differentiated liposarcomas (ALT/WDL); however, the implications and specific indications for use are not well-established in the current literature. Herein, we extend previous findings by quantitatively evaluating the impact of molecular testing of lipomatous neoplasms in our routine clinical practice, how it modifies the historical perspective of their clinical course, and the effect of distinct surgical procedures in modulating the risk of local recurrence for these tumors after molecular classification. On the basis of these analyses, we suggest a specific set of basic recommendations for complementary molecular assessment in the diagnosis of lipomatous tumors. Four hundred and five lipomatous neoplasms located in the trunk and extremities were analyzed histologically and for the presence of 12q13-15 amplification on paraffin-embedded tissues by assessing *MDM2*/*CPM* amplification. Survival analyses were calculated with Kaplan-Meier and compared with the log-rank. Multivariate analysis was evaluated by the Cox regression method. The 405 tumors were histologically classified as ordinary lipoma (n = 324), intramuscular lipoma (n = 29), and ALT/WDL (n = 52). The level of agreement between the histologic diagnosis and the molecular diagnosis was high (96%) but pathologists showed a tendency to overestimate cytologic atypia and the diagnosis of ALT/WDL (precision, 79%; accuracy, 88%). Molecular assessment led to a major diagnostic reclassification in 18 tumors (4%). Eleven of the tumors histologically classified as ALT/WDL were reclassified as ordinary lipoma (n = 5) and intramuscular lipoma (n = 6); none of which recurred. Seven ordinary lipomas were reclassified as ALT/WDL, 6 of which were larger than 15 cm and deeply located; 2 recurred locally. After molecular data, the 5-year local recurrence rates for ordinary lipoma, intramuscular lipoma, and ALT/WDL were 1%, 12%, and 44%, respectively. Multivariate analyses after molecular assessment showed tumor type and type of resection to be associated with the risk of local recurrence. Complementary molecular testing refines the histologic classification of lipomatous tumors and better estimates the impact of surgical procedures on the risk of local recurrence. Pathologists tend to overestimate the degree of cytologic atypia and the indiscriminate use of molecular testing should be avoided, especially for extremity-based tumors. Molecular testing should be considered for "relapsing lipomas," tumors with questionable cytologic atypia (even if widely excised), or for large lipomatous tumors (> 15 cm) without diagnostic cytologic atypia.

Key Words: lipoma, atypical lipomatous tumor/well-differentiated liposarcoma, molecular analysis, diagnosis, prognosis

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Lipomatous neoplasms represent the largest subgroup of mesenchymal neoplasms and are commonly encountered by primary care clinicians, clinical oncologists, surgeons, and pathologists.[20,28,29] The classification of these neoplasms has historically been based on histologic features.[18] This can be problematic in the discrimination of lipoma from atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL), especially those with subtle cytologic atypia or so-called lipoma-like histology.[1,11,17,36]

Cytogenetic and molecular genetic studies have provided insight into the pathogenesis of various benign and malignant lipomatous tumors. Lipomas are commonly characterized by rearrangements of the chromatin remodeling gene *HMGA2* on chromosome 12q15.[3,28] In contrast, ALT/WDL have been shown to contain amplified sequences primarily derived from chromosome bands 12q13-15, usually in the form of giant marker and ring chromosomes. This amplicon contains several genes

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including *MDM2, CPM, HMGA2, CDK4*, and *SAS*, among others.[2,8,11,13,17,24,26,27,29,31,32,35,36] On the basis of these distinct molecular profiles, several studies have shown that complementary molecular analysis is useful to discriminate lipomas from ALT/WDL.[11,17,27,31,32,35,36]

Our group has been consistently evaluating these tumors at the molecular level for the last 5 years with more than 600 tumors analyzed. During these years many questions from pathologists, surgeons, and clinical oncologists arose in regard to the use of complementary molecular analysis for the diagnosis of lipomatous tumors. Surprisingly, many of these questions have not been answered sufficiently by the currently available literature. Below are representative examples of questions raised by colleagues, which are addressed in the present study:

1. What is the clinical course (local recurrence rates) for molecularly confirmed ordinary lipomas, intramuscular lipomas, and ALT/WDL?
2. Is there value in performing molecular assessment if the lesion was widely excised? Does it change anything?
3. In tumors with no cytologic atypia, when should molecular testing be ordered? Is there a size criterion?
4. Using clinical outcomes as the gold standard, how accurate are we in diagnosing these tumors by histologic assessment alone? Which one correlates the best, molecular testing or histologic assessment?
5. How do we define cytologic atypia or questionable cytologic atypia?

It is assumed that the answer to the first question is well established but reading the literature reveals the opposite. According to rare studies, the local recurrence rate for ordinary lipoma is $< 2\%$[7,30]; however, local recurrence rates for intramuscular lipoma and ALT/WDL are reported to range from 3% to 63% and from 5% to 52%, respectively.[4,5,7,10,12,14,19–21,30,33,37] These widely variable and overlapping numbers may be explained by many factors, including population heterogeneity, anatomic location, tumor size, type of excision/resection, and distinct diagnostic criteria. Therefore, local recurrence rates for molecular-confirmed lipomatous tumors are not established, as most of these studies were based on histologic assessment alone.

Similarly, no study has addressed the second and third questions. The second question is commonly raised by surgeons who specifically want to know the local recurrence risks for widely excised lipomas and ALT/WDL. The answer to the third question is not specifically addressed in the literature. As far as we know no study has systematically used clinical outcomes adjusted to surgical procedures to evaluate the diagnostic power of histologic and molecular assessments. Indeed, some have correlated the molecular reclassification of lipomatous tumors to individual outcomes but have not extrapolated the data in a systematic fashion or compared the clinical outcomes based on histologic assessment and molecular assessments.[32] Additionally, a few studies have used primarily standard cytogenetic data,[5,7] which can be biased to the common problem of growing non-neoplastic cells or culture failures in a substantial number of cases. Furthermore, standard cytogenetic analysis is unavailable in most centers. The fourth and fifth questions are somewhat related. Molecular assessment may help with the diagnosis of lipomatous tumors and many studies have addressed this point.[6,11,17,27,31,32,35,36] However, we still do not know how precise and accurate we are in diagnosing these tumors at the histologic level; test-based properties such as sensitivity, specificity, accuracy, and precision of the histologic diagnosis when compared with molecular assessment have not been determined; these studies also help in answering the subjective issue of defining cytologic atypia. Despite the fact that it is extremely challenging to define what cytologic atypia should be, this should not preclude us to further explore the implications of this subjective uncertainty.

In summary, we propose with this study to critically evaluate the impact of molecular assessment in the diagnosis of lipomatous tumors and suggest a set of guidelines for optimization of its use.

MATERIALS AND METHODS

Patients

This study was approved by the Mayo Clinic Institutional Review Board. Four hundred and fifty-nine cases of lipomatous neoplasms located in the trunk and extremities from the Mayo Clinic patient files from January 1990 to December 2000 were selected for this study. Radiology reports or images (311) were available for all the tumors. All tumors were treated by complete excision or resection. Surgical excision were considered marginal if the surgical margins were < 1 cm and wide if ≥ 1 cm at the time of surgery. Retroperitoneal tumors were excluded due to their distinct clinical behavior and treatment.[16,22,23] From these 459 tumors, slides and tissue materials for histologic and molecular analyses were available for 405 tumors. The average number of slides evaluated per case was 8 (range, 3-147). Considering that the median tumor size was 6 cm, more than 1 slide was available for each cm of tumor length. Ordinary lipomas, intramuscular lipomas, and ALT/WDL were included in this study and other less common types of lipomatous tumors were excluded. The tumors were histologically classified by 3 pathologists with soft-tissue tumor pathology expertise (A.M.O., H.Z., and A.G.N.) and a general surgical pathologist (R.Q.Z.) according to the 2002 World Health Organization criteria.[9,25] Focal cytologic atypia was arbitrarily defined as 1 or less atypical cell/slide/tumor.

Fluorescence In Situ Hybridization

Owing to material availability, tissue from 405 tumors was submitted for molecular analysis. Paraffin-embedded tissue representative of the neoplastic components was used for fluorescence in situ hybridization

analysis to identify amplification of *CPM* and *MDM2* located on chromosome band 12q15.

All 405 cases were evaluated with laboratory-developed fluorescence in situ hybridization probe sets for both *CPM* (carboxypeptidase M) and *MDM2*. Bacterial artificial chromosomes (BAC) for *CPM* have been previously described.[11] BAC clones spanning the *MDM2* locus were obtained from the Children's Hospital Oakland Research Institute (Oakland, CA) and include: RP11-61F20, RP11-816C9, RP11-185H13, RP11-450G15. All the identities of the BAC clones were confirmed by polymerase chain reaction and by hybridization on metaphase preparations from the peripheral blood of 5 normal individuals. Analytical sensitivity and specificity of each probe was calculated and their performance on paraffin-embedded tissue was verified on numerous normal tissue types, including skeletal muscle, adipose tissue, and others. Amplification was defined as *CPM* or *MDM2* signals/CEP12 ratio ≥ 3. Normal structure readily identified under the 4′, 6-diamidino-2-phenylindole (DAPI) staining on thin sections such as blood vessels and epidermis were used as internal controls for the cases analyzed. Normal signal patterns were established by scoring 100 cells from each normal tissue.

DNA isolation was performed using the Qiagen Plasmid Maxi kit (Qiagen, Valencia, CA). DNA was labeled using a nick translation kit (Abbott Laboratory, North Chicago, IL). Interphase molecular cytogenetic studies were performed using 4-μm paraffin-embedded thin sections that were deparaffinized twice in xylene (15 min pretreatment), dehydrated once in 100% ethanol (5 min), and treated with 10 mmol/L citric acid (10 min, in a humidified microwave). Tissue sections were incubated in warm (37°C) sodium chloride-sodium citrate buffer (2 × SSC) for 5 minutes. Protein was digested with Digest-All 3 (Invitrogen Corporation, Carlsbad, CA). After a brief wash in phosphate-buffered saline (1 × PBS), slides were sequentially dehydrated in ethanol (70%, 80%, 100%), and air-dried at room temperature. Tissue sections were denatured at 85°C for 5 minutes, and BAC probe hybridization was performed overnight in a humidified chamber at 37°C. Tissue sections were washed in 0.1% Nonidet P-40 in 2 × SSC at 76°C for 2 minutes and then rewashed in the same solution at room temperature for 1 minutes. Slides were mounted in Vectashield mounting medium (Vector Labs, Burlingame, CA) with 1.5 μg/mL DAPI medium (Vector Labs).[34] Tumor samples were considered positive if more than 10% of 100 cells analyzed showed amplification. Tumors were evaluated and scored by 2 independent investigators.

Statistical Analysis

Summary statistics were obtained by using standard methods. The local recurrence-free survival was estimated with the Kaplan-Meier method, and the survival curves were compared using the log-rank test. Multivariate analysis was conducted with Cox proportional hazards regression model. The variables, including tumor size (≤ 5 cm, > 5 cm), histologic type (ordinary lipoma, intramuscular lipoma, ALT/WDL), depth (superficial, deep), and type of resection (local excision, wide excision), were entered into the multivariate model. Statistical significance was defined as $P < 0.05$ (2-tailed). All statistical analyses were performed with SAS 8.2 software.

RESULTS

Clinical Features

The cases included 213 females and 192 males (ratio: 1.1:1). The median age at the diagnosis was 57 years. All tumors were located in the trunk and extremities: 125 in the thighs and buttocks, 133 in the arms and shoulders, 40 in the forearms, 30 in the legs, 8 in the trunk and back, 42 in the hands and feet, with the remainder in other random sites. Tumor size ranged from 1 to 45 cm (median, 6 cm). If multiple tumors were present, the largest tumor was used for the analysis. Two hundred and nineteen tumors were located above the superficial fascia and 140 were located deeper than the superficial fascia. The remaining tumors apparently extended to both sides of the superficial fascia and their primary origin could not be determined with certainty. All tumors were completely excised with reported negative margins. Wide local excision was performed for 35 tumors (before molecular classification: 5 ordinary lipomas, 1 intramuscular lipoma, 29 ALT/WDL; after molecular classification: 6 ordinary lipomas, 3 intramuscular lipomas, 26 ALT/WDL).

Pathologic Features and Molecular Reclassification

All tumors were initially evaluated solely by histology. The 405 tumors were histologically classified as ordinary lipoma (n = 324), intramuscular lipoma (n = 29), and ALT/WDL (n = 52). Among the ALT/WDL, most exhibited a lipoma-like histology (n = 46); 4 tumors displayed sclerosing features, and 2 a prominent inflammatory component. An average of 5, 6, and 9 slides was reviewed for each tumor category, respectively. Molecular cytogenetic evaluation for *MDM2*/*CPM* amplification was performed on these tumors independently by 2 technologists blinded to the histologic diagnosis. On the basis of the presence or absence of *MDM2*/*CPM* amplification, the 405 tumors were reclassified as *MDM2*/*CPM*-nonamplified (n = 357) and *MDM2*/*CPM*-amplified (n = 48). As previously observed by our group,[11] all *CPM*-amplified tumors also showed *MDM2* amplification. Similarly, all *CPM*-negative tumors were also negative for *MDM2* amplification. Under the premise that *MDM2*/*CPM*-nonamplified tumors should represent ordinary lipomas and intramuscular lipomas, all of the nonamplified cases were rereviewed histologically and reclassified as ordinary lipoma (n = 322) and intramuscular lipoma (n = 35). Eleven of the 52 tumors (21%) histologically classified as ALT/WDL (all with lipoma-like histology) were reclassified into ordinary lipoma (n = 5; 10%) and intramuscular lipoma (n = 6; 12%)

TABLE 1. Classification of Lipomatous Tumors Before and After Complementary Molecular Analysis for *CPM/MDM2*

	Before Molecular Analysis			
After Molecular Analysis	**Lipoma**	**IM Lipoma**	**ALT/WDL**	**Total**
IM Lipoma	0	29	6	35
Lipoma	317	0	5	322
ALT/WDL	7	0	41	48
Total	324	29	52	405

ALT/WDL indicates atypical lipomatous tumor/well-differentiated liposarcoma; IM, intramuscular.

(Table 1 and Fig. 1); none recurred. Upon rereview, these tumors showed subtle cytologic atypia with mild or equivocal nuclear hyperchromasia (Fig. 1B). An average of 7 slides per tumor was available for the review. Conversely, 7 of the 324 tumors (2%) histologically classified as ordinary lipoma were reclassified as ALT/WDL (Table 1, and Fig. 1). These tumors showed no cytologic atypia but tended to be deep and sizable tumors (6/7 were larger than 16.5 cm and deep seated; a single example was superficial and measured 8 cm in greatest dimension; Figs. 1C, D). Two of the deeply seated tumors recurred locally. An average of 8 slides per tumor was available for review.

Using the molecular status of these tumors as a gold standard to differentiate benign from malignant lipomatous tumors, we verified that the sensitivity, specificity, positive predictive value (precision), negative predictive value, and accuracy of histologic evaluation were 85%, 97%, 79%, 98%, and 88%, respectively.

Survival Analysis

Complete clinical data including follow-up information was available for 303 specimens (75%). Median follow-up was 108 months (range, 1-211 mo). Twenty-three patients presented with local recurrence between

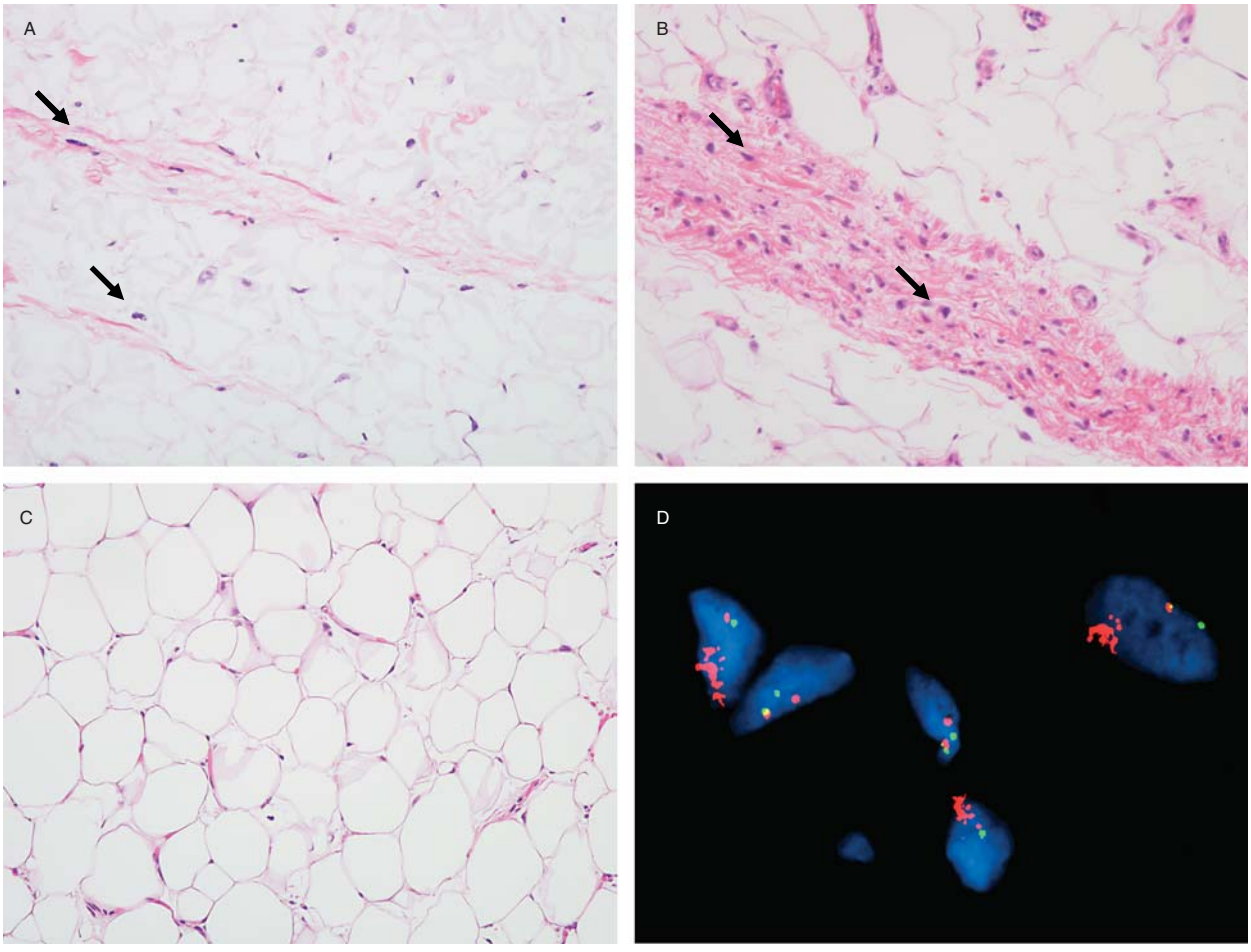

FIGURE 1. Histologic features of an ALT/WDL (A) with rare atypical hyperchromatic cells (arrows), a lipoma (B) with reactive cytologic atypia (arrows) that was negative for *CPM* amplification, and a recurrent ALT/WDL without cytologic atypia (C) that was shown to contain both *CPM* and *MDM2* amplification (D; *CPM*, orange signals; CEP12, green signal). The common histologic overlap among these 2 groups of neoplasms often leads to diagnostic dilemmas. ALT/WDL indicates atypical lipomatous tumors/well-differentiated liposarcomas.

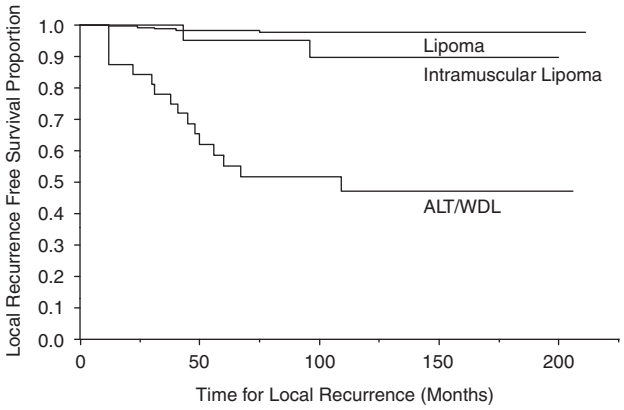

FIGURE 2. Comparative Kaplan-Meier survival curves for trunk and extremity-based lipomatous neoplasms classified according to histologic assessment (log-rank, $P < 0.0001$).

12 and 109 months (median, 40 mo) at the time of last follow-up. None of the patients died due to disease. Figure 2 shows the local recurrence-free survival curves for the 3 groups of lipomatous tumors before molecular classification (histologic classification only). Median survival was reached only with ALT/WDL (median, 109 mo). The local recurrence rates of ordinary lipoma, intramuscular lipoma, and ALT/WDL were 2%, 5%, and 45%, respectively ($P < 0.0001$). Figure 3 shows the local recurrence-free survival for the 3 groups after molecular reclassification and histology reevaluation. Median survival was not reached in any of the 3 groups. The local recurrence rates of ordinary lipoma, intramuscular lipoma, and ALT/WDL were 1%, 12%, and 44%, respectively ($P < 0.0001$). In both classifications, the lowest recurrence rate was observed for ordinary lipoma, the highest recurrence rate for ALT/WDL, and intramuscular lipoma showing an intermediate risk. However, after molecular data were incorporated into the classification scheme, the 3 groups segregated into more clearly defined risk groups.

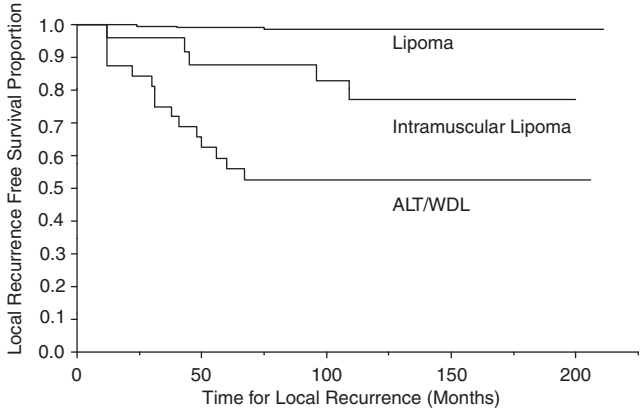

FIGURE 3. Comparative Kaplan-Meier survival curves for trunk and extremity-based lipomatous neoplasms reclassified after complementary molecular assessment. Observe that the clinical course among the 3 groups of tumors is better discriminated (log-rank, $P < 0.0001$).

Multivariate Analysis of Prognostic Factors

Multivariate analysis of prognostic factors for local recurrence in patients with lipomatous tumors is shown in Table 2. Before molecular classification, histologic type emerged as the only independent risk factor for local recurrence [$HR_{alt} = 3.69$; 95% confidence interval (CI), 1.68-9.09; $P = 0.0002$]. ALT/WDL presented the highest rate of local recurrence. The other factors investigated (tumor size, depth, or type of resection) did not reach statistically significant levels. However, after molecular data were integrated into the classification, multivariable analysis confirmed that both histologic subtype ($HR_{alt} = 2.63$; 95% CI, 1.29-5.61, $P < 0.0001$), and type of resection ($HR_{wle} = 0.59$; 95% CI, 0.36-0.96; $P = 0.0359$) correlated independently with the risk of local recurrence.

DISCUSSION

Lipomas and liposarcomas are among the most common mesenchymal tumors. Lipomas account for nearly one-half of all benign mesenchymal lesions and ALT/WDL represent one of the most common types of sarcoma.[20,28,29] ALT/WDL are typically differentiated from lipomas histologically by the identification of hyperchromatic atypical cells or atypical lipoblasts. However, in certain cases, these cells may be rare or absent, which results in a common diagnostic dilemma.[6] In contrast, lipomas may exhibit Lochkern effect and secondary changes such as inflammation, fibrosis, and necrosis, or induce peritumoral secondary muscle atrophy which may be mistaken for the atypical features seen in ALT/WDL.[1,11,17,36] Therefore, it is not a surprise that lipoma and its variants have been reported to be one of the most frequent benign mesenchymal lesions misdiagnosed as sarcomas.[1,15] Our study not only agrees with these findings but also found that pathologists are better in diagnosing lipomas than ALT/WDL with a specificity of 97% and negative predictive value of 98% when molecular testing is used as "the gold standard" calibrator. These findings can be explained by the much higher prevalence of lipomas and our natural tendency to overestimate cytologic atypia in a difficult diagnostic setting. In other words, in spite of the fact that we cannot define what "cytologic atypia" is or should be, we can state that when dealing with a situation of "questionable cytologic atypia", most likely these cases will not result in a diagnosis of ALT/WDL when confirmatory molecular assessment is applied. In our practice over the last few years, in the vast majority of cases in which cytologic atypia was questioned in a lipomatous tumor, molecular analysis did not corroborate the diagnosis of ALT/WDL. Our low precision (79%) and overall accuracy (88%) for the diagnosis of ALT/WDL also supports this impression.

As noted above we used the molecular status as a calibrator for assessing our histologic diagnostic abilities

TABLE 2. Risk for Local Recurrence of Lipomatous Neoplasms Before and After Complementary Molecular Assessment for *CPM/MDM2*

	Before Molecular Analysis Univariate Analysis*, Multivariate Analysis†				After Molecular Analysis Univariate Analysis*, Multivariate Analysis†			
	P	*P*	HR	95% CI	*P*	*P*	HR	95% CI
Tumor size > 5 cm	0.0004	0.1987			0.0004			
ALT/WDL‡	< 0.0001	0.0002	3.69	1.68-9.09	< 0.0001	< 0.0001	2.63	1.29-5.61
Deep tumor	< 0.0001	0.9188			< 0.0001			
Wide local excision	< 0.0001	0.1749			< 0.0001	0.0359	0.59	0.36-0.96

*Log-rank test.
†Cox regression model.
‡Defined as MDM2/CPM-positive cases for molecular analysis.
ALT/WDL indicates atypical lipomatous tumor/well-differentiated liposarcoma; CI, confidence interval; HR, hazard ratio.

for lipomatous tumors. Additionally, because tumor classification schemes using patient outcome data as the initial framework are likely to be the most clinically useful, we compared the clinical outcome of lipomatous lesions based on histologic assessment only, and after the use of complementary molecular assessment. In our cohort the 405 tumors were histologically classified into ordinary lipoma/intramuscular lipoma (n = 353) and ALT/WDL (n = 52). The same group was also independently classified according to molecular status into *MDM2*/*CPM*-nonamplified (n = 357) and *MDM2*/*CPM*-amplified (n = 48) tumors as the molecular classification cannot discriminate between ordinary lipoma and intramuscular lipoma. All cases with visible and diffuse cytologic atypia universally showed *MDM2*/*CPM* amplification. However, *MDM2*/*CPM* amplification was detected in 7 of 324 tumors (2%) initially categorized as ordinary lipoma by histologic evaluation only. Upon review, these tumors showed no detectable cytologic atypia but follow-up information available from 6 patients showed local recurrences in 2 instances. Conversely, among 5 "relapsing lipomas" diagnosed by histologic assessment, 2 were reclassified into ALT/WDL based on *MDM2*/*CPM* status. Moreover, among all 52 tumors histologically classified as ALT/WDL, 11 were reclassified into ordinary lipoma or intramuscular lipoma due to absence of *MDM2*/*CPM* amplification; none of these experienced local recurrences. Upon review, all 11 cases showed focal cytologic atypia. *CPM* and *MDM2* results agreed for all cases evaluated. These findings support the impression that histologic assessment remains the cornerstone for the diagnosis of these tumors but that complementary molecular reclassification refines the results obtained with histologic evaluation alone in predicting the clinical course of these patients, especially if no cytologic atypia is present. Therefore, it seems that molecular testing is appropriate for relapsing tumors initially diagnosed as lipomas or for tumors with questionable cytologic atypia (in this last scenario with the preknowledge that the diagnosis of ALT/WDL will not be supported in most cases after molecular characterization). However, new light was shed on an important issue that is omitted from the literature: the diagnosis of ALT/WDL that does not contain apparent cytologic atypia. Although it is impractical and costly to perform molecular analysis for all lipomatous tumors without cytologic atypia located in the trunk and extremities, a strategy to avoid missing these clinically significant tumors is needed due to their higher risk of local recurrence. Among the 7 cases without cytologic atypia classified as ALT/WDL after molecular analysis, 6 were very large tumors (> 16.5 cm) and deep seated; the exception was a superficial tumor measuring 8 cm in greatest dimension. Therefore, our data suggest molecular testing to be useful for all deep seated and larger lipomatous tumors (> 15 cm) without cytologic atypia to exclude the possibility of ALT/WDL (Table 3).

As previously stated, the local recurrence rate for an ordinary lipoma is very low.[7,30] However, local recurrence rates for intramuscular lipoma and ALT/WDL range widely.[4,5,7,10,12,14,19–21,30,33,37] Our results confirm the impression that ordinary lipomas rarely recur (1%); however, the local recurrence rates for intramuscular lipomas and ALT/WDL are quite distinct. Intramuscular lipoma recurs in 12% of cases and WDL/ALT recurs in 44% of cases.

Another very important question omitted from the literature was to assess the clinical impact of the surgical procedure on the utility of molecular classification. In other words, does molecular assessment change management if the tumor has already been widely excised? Multivariate analysis showed that before molecular classification, only histologic type was significantly associated with the risk for local recurrence. However,

TABLE 3. Indications for Molecular Analysis for Lipomatous Tumors

Lipomatous tumors with equivocal cytologic atypia
Recurrent "lipomas"
Deep seated lipomatous tumors without cytologic atypia larger than 15 cm
Retroperitoneal (or intra-abdominal) lipomatous tumors without cytologic atypia*

*See Ref. 23.

after complementary molecular testing, type of surgery gained significance as an independent prognostic factor for minimizing the risk of local recurrence; wide local excision of a lipomatous tumor decreased the risk for local recurrence by almost half. These findings imply that complementary molecular classification refines the contribution of individual variables in relationship to the local recurrence risk, possibly influencing important therapeutic decisions.

In summary, complementary molecular testing refines our classification of lipomatous tumors and better defines the impact of surgical procedures on the risk of local recurrence for these tumors. Pathologists tend to overestimate the degree of cytologic atypia; therefore, familiarity with classic artifacts seen in lipomatous tissues should be advocated to avoid the indiscriminate use of unnecessary molecular testing, especially for extremity-based tumors. In addition to retroperitoneal tumors,[23] molecular testing should be used for "relapsing lipomas," questionable cytologic atypia (even if widely excised), or for large lipomatous tumors (> 15 cm) without cytologic atypia.

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